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JOHN FITCH LANDON, M.D., Editor

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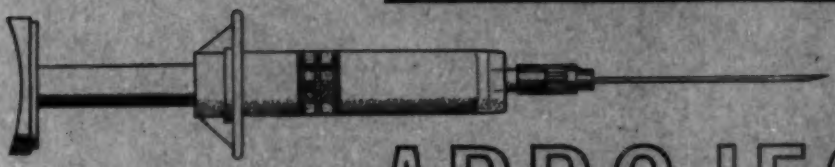

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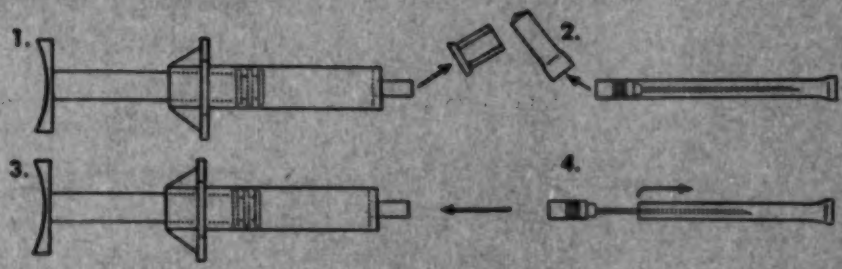

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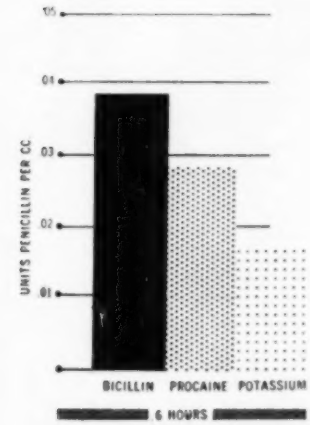

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ARCHIVES OF PEDIATRICS

VOL. 69 SEPTEMBER 1952 No. 9

JOHN FITCH LANDON, M.D., Editor

IMPROVEMENT IN PROTEIN EFFICIENCY OF A WHOLE WHEAT CEREAL BREAKFAST FOOD WITH THE AMINO ACIDS LYSINE AND THREONINE AND VITAMIN B_{12}*

BARNETT SURE, Ph. D.
Fayetteville, Ark.

Half of the world's people derive more than half of their calories from the cereals. The cereal grains also provide the cheapest source of proteins and are the main source of nourishment for peoples with low income levels. However, the proteins of wheat are deficient in the amino acid lysine, and the proteins of corn in lysine and tryptophane.[1] When the cereal grains are supplemented with a sufficiency of meats, dairy products and eggs, such amino acid deficiencies are prevented, but people of low income levels cannot afford to have an adequacy of these animal foods and hence enrichment of cereal grains promises a more economical and nutritious diet for large populations of the world, i. e., in the South where protein and vitamin deficiencies exist; in the Latin American countries, whose populations derive a large proportion of their proteins from corn; and in the Orient where 70 to 85 per cent of the proteins are derived from rice.

Artificial enrichment of flour must be regarded as a useful supplement to correct outstanding shortages created by bad food habits and by economic pressure on the poor. In this country,

*From the Department of Agricultural Chemistry, University of Arkansas, Fayetteville, Ark.
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over one-half of the states have enriched flour programs and legislation for vitamin enrichment of flour is pending in additional states. Enriched white flour contains per pound not less than 2 mg. of thiamine, 1.2 mg. riboflavin, 16 mg. niacin, and 13 mg. iron. Lane, Johnson and Williams[2] estimated that, if the use of enriched flour becomes universal, the average intake will be increased about 64 per cent. If in large scale production of amino acids the cost can be reduced to an extent that it becomes economical for further enrichment of flours and cereal grains and food products derived therefrom, we can anticipate large scale reductions of malnutrition in this country and abroad. A beginning along this line has already been made. The sulfur-containing amino acid, methionine, is now being produced so cheaply that it is being used economically in the feeding of poultry.

Heat processing is known to affect the nutritive value of proteins in various ways. The adverse effect of heat on dietary proteins has been recently reviewed.[3, 4] In 1943, information became available on the influence of extreme heat, applied for a short time, on the biological value of the proteins in cereal breakfast foods. Stewart, Hensley and Peters[5] have shown that in feeding experiments on growing rats that the ratio of gain in body weight to protein consumed is depressed by two-thirds by the gun explosion of an oats-corn-rye mixture, and by three-fourths by the gun explosion of oats alone. In this connection, Mitchell, Hamilton and Beadles[6] state: "In the public interest, it would seem to be desirable to process cereals for human consumption by methods which are less destructive of nutrient content." Melnik and Oser,[4] however, have shown that when cereals are properly cooked no undesirable changes in the protein component occur and their nutritive value appears to be equal to that of the unheated protein. Beaudoin, Mayer and Stare[7] reported that the cooking of whole wheat as in the preparation of shredded wheat, under optimum conditions, results in a significant improvement in the nutritional value of whole wheat.

Recently the author[8] investigated the nutritional values of proteins in various cereal breakfast foods and found that some of those which are used most have the poorest biological values. Among the best from the standpoint of protein efficiency are oatmeal, Instant Ralston and the infant foods Cerevim and Pablum.

Since breakfast foods are generally eaten with liberal supplies of milk which furnish the amino acid deficiencies in the cereals, the question arises: Of what importance is it to know which breakfast food is of excellent, good, or poor protein quality?[9] For a logical answer we must consider the following: A normal individual loses 20 to 30 gm. of proteins daily as a result of "wear and tear" of broken down tissues.[10] Therefore, of a daily intake of 70 gm. (which is the daily requirement recommended by the Food and Nutrition Board of the National Research Council), there are left 40 to 50 gm. for growth, blood formation, production of enzymes and hormones, and for resistance to infections. Of all the proteins ingested, only those of animal origin are considered to be of superior biological value. These constitute about 55 per cent of the total protein consumption. After the amount needed for repair of body tissues has been subtracted, there are left only 25 gm. of good quality proteins for the performance of all vital physiological functions. Therefore, when there is a choice between eating a breakfast food of poor protein quality and one of superior, the latter has the advantage of providing better quality nitrogen for wear and tear of tissue and for growth, and the milk could then supply valuable nitrogen for such functions as blood formation, hormones, enzymes and antibodies. Milk and the proteins from an overheated cereal breakfast food will not do it. For people who are unable to purchase a sufficiency of the more expensive foods of animal origin, it would, therefore, be advisable, when they use breakfast foods, to choose those containing proteins of superior biological value.[8]

Our recent finding that the proteins of whole wheat can be improved considerably with the amino acid threonine[11] and the protein efficiency of an infant food can be improved with minute amounts of crystalline vitamin B_{12},[12] stimulated the addition of this amino acid and vitamin to a processed whole wheat breakfast food.*

This study was conducted on the Wistar strain albino rat. The animals were 28 days old when started on the experiments and weighed 50 to 55 gm. each. The sexes were equally divided. There were 12 animals in each group but, because of considerable in-

*The breakfast food used was Wheaties purchased from a local wholesale grocery.

dividual variations in growth, the control groups without amino acid additions had 24 animals.

The breakfast food contained 10 per cent protein and was incorporated to the extent of 8 per cent in the rations. The rations contained, percentagely, 80 of the breakfast food; 2 of cellu flour for roughage; 4 of Sure's salts No. 1[13]; 3 of vegetable shortening; 2 of cod liver oil; 1 of wheat germ oil, and the rest cerelose (glucose).

Since Light and Frey[14] found that the proteins in white and whole wheat breads can be further improved by supplementing the lysine with valine, the latter amino acid was also added to the basal ration. Threonine additions were made in the presence of lysine and valine.

In 1949 King and Hauge[15] reported on the existence of an unidentified fourth factor in condensed fish solubles (a by-product from the fish meals industry) which is distinct from the chemically defined vitamins and amino acids. In this investigation the addition of the liquid portion of a fish soluble product was also used in amounts equivalent to 5 per cent of the raw material in the ration. It was poured on the cerelose and contributed 0.196 per cent foreign nitrogen in the ration. No attempt was made at concentration.*

The fat-soluble vitamins A, D and E were provided by the cod liver oil and wheat germ oil in the rations. The following crystalline components of the vitamin B complex were administered six times weekly to each animal separately from the ration: 25 μg. each of thiamine, riboflavin, pyridoxine, and niacin; 150 μg calcium pantothenate, 3 mg. p-aminobenzoic acid, 6 mg. choline chloride, and 1 mg. inositol. From the gains in body weight per gram of protein intake the protein efficiency ratios (PER) were calculated.

The results of this investigation are summarized in Table 1. It will be noted from this table that when whole wheat served as the only source of proteins in the ration at an 8 per cent protein level the average gain in body weight per animal during a six weeks period was 40.9 gm., while on a ration which supplied the same

*After completion of this study it was found that one-half of the nitrogen could be removed by precipitation with five volumes of 95 per cent ethyl alcohol in an insoluble residue.

protein content from the processed whole wheat breakfast food there was a loss of 0.8 gm. per animal during that period, which indicates that the proteins in the breakfast food were injured during processing. The supplementation of the basal ration with 0.1 μg vitamin B_{12} per animal per day was of no benefit. The addition

TABLE 1. *Influence of Addition of Amino Acids, Vitamin B_{12}, and a Fish Soluble Extract on the Efficiency of the Proteins in a Whole Wheat Cereal Breakfast Food. Fed at an 8 per cent protein level for six weeks (average results per animal)*

Type of Ration	Ration Number	Changes in Body Weight (gm.)	Total Food Intake (gm.)	Protein Intake (gm.)	Protein Efficiency Ratio (PER)[2]	SD[3]
Whole Wheat	1	+ 40.9	418.7	33.5	1.22	±.08
Whole Wheat Breakfast Food (W.W.B.F.)	2	— 0.80	225.7	18.1	—0.04	±.02
W.W.B.F.+0.1 μg B_{12}[4]	3	— 0.83	221.8	17.7	—0.05	±.03
W.W.B.F.+0.4% l-lysine	4	+ 50.9	344.4	27.6	1.84	±.08
W.W.B.F.+0.4% l-lysine +0.5% dl-valine	5	+ 47.8	347.1	27.7	1.73	±.07
W.W.B.F.+0.4% l-lysine +0.5% dl-valine +0.2% dl-threonine	6	+ 63.9	381.4	30.5	2.10	±.13
W.W.B.F.+0.4% l-lysine +0.5% dl-valine +0.2% dl-threonine +0.1 μg B_{12}[4]	7	+ 81.8	455.2	36.4	2.25	±.09
W.W.B.F.+0.4% l-lysine +0.5% dl-valine +0.2% dl-threonine +fish soluble extract	8	+ 80.4	397.7	31.8	2.53	±.11
W.W.B.F.+0.4% l-lysine +0.5% dl-valine +0.2% dl-threonine +fish soluble extract +0.1 μg B_{12}[4]	9	+106.6	477.4	38.2	2.79	±.13

[1]Wheaties.
[2]Expressed as gains in body weight per gram of protein intake.
[3]Standard deviation.
[4]Per animal per day.

of 0.4 per cent l-lysine monohydrochloride to this ration resulted in remarkable growth and in increase in protein efficiency, which was superior to that obtained on the proteins furnished by the unheated whole wheat. The further addition of 0.5 per cent dl-valine in the ration resulted in a slight inhibitory effect on growth. However, the addition of as little as 0.2 per cent dl-threonine, which introduced only 0.024 per cent additional nitrogen in the

ration, was accompanied by 33.7 per cent greater growth and 21.4 per cent increase in PER. The further supplementation of this ration with 0.1 μg vitamin B_{12} per animal per day was followed by 28 per cent additional growth, largely due to increased food consumption, the PER being increased only by 7.1 per cent. The introduction of the fish soluble extract produced no further increase in body weight but in 12.2 per cent increase in PER, because about the same increase in weight was produced on lesser food intake. A most marked further increase in body weight and protein efficiency, however, was obtained when 0.1 μg vitamin B_{12} was administered daily to each animal in presence of the fish soluble extract. Compared with ration 8, the minute amounts of vitamin B_{12} in ration 9 produced 32.6 per cent increased growth, 19.3 per cent increase in food consumption, and 10.3 per cent in PER. It should be noted that the only difference between rations 9 and 7 is that ration 9 contained the fish soluble extract; therefore, the results may be also interpreted that the foreign nitrogen in the fish soluble extract supplemented ration 7. To summarize, the data in Table 1 indicate that vitamin B_{12} supplements ration 6, in the presence of lysine, valine and threonine; and that this vitamin also supplements ration 8 containing these amino acids and the fish soluble extract; but at the same time the foreign nitrogen in the fish soluble extract supplements ration 7, containing lysine, valine, threonine, and supplied with vitamin B_{12} administered to the animals separately from the ration. Because we did not concentrate the condensed fish solubles and because of its high nitrogen content, we attribute its influence on growth to its foreign nitrogen rather than to its furnishing an unidentified growth factor.

In this study we did not make any additions of threonine in the absence of valine. It is possible then that valine made no contribution in this experimental set-up.

The significant fact in this investigation is that a whole wheat cereal breakfast food, which was so markedly injured during processing, as evidenced by absolute lack of growth when it furninshed all the proteins in the ration, could be so tremendously improved in protein efficiency by minute additions of the amino acids, lysine and threonine, by traces of vitamins B_{12}, and by small amounts of nitrogen furnished by a fish soluble extract. These results may have extensive human application when the amino acids used in

this investigation can be produced as economically as many of the crystalline vitamins of the B complex.

SUMMARY

Considerable improvement in the protein efficiency of a whole cereal breakfast food was obtained by the addition of 0.4 per cent l-lysine monohydrochloride, 0.2 per cent dl-threonine in the ration, 0.1 μg of crystalline vitamin B_{12} per animal per day, and an extract from condensed fish solubles which introduced 0.196 per cent nitrogen in the ration.

We wish to express our appreciation to Merck & Company for the crystalline vitamin B_{12} used in this study.

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METHIONINE IN LIPOID NEPHROSIS

A Therapeutic Trial

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I. *Definition.* The clinical picture of lipoid nephrosis is well-known and has been frequently described in medical literature. Lipoid nephrosis is an uncommon disease of children in which there is a massive albuminuria, with low plasma protein, reversal of the albumin-globulin ratio in the blood, marked edema, hypercholesteremia, increased susceptibility to infection, low basal metabolism and absent hypertension. The syndrome usually has a chronic and sometimes a prolonged course, which may be marked by exacerbations and remission.

II. *Treatment.* The treatment of nephrosis is still mainly symptomatic but some progress has been made in handling symptoms. Many treatments for the outstanding symptom of edema are in use, including ephedrine, thyroid, mercurial diuretics, penicillin (during periods of pyrexia), urea, ion-exchange resin,[1] fever, typhoid vaccine and ACTH. Janeway and his associates[2] ascribe the improved prognosis in their young patients to the control of intercurrent infections. They further state that no form of treatment has been found wholly satisfactory.

The most serious symptom requiring treatment is massive edema, usually with ascites. This is a result of hypo-albuminemia, but factors are involved which are not clearly understood. The edema is often difficult to control for diuretics may or may not be effective. Urea is a difficult drug to give but is unlikely to harm the kidneys. Mercurial diuretics with ammonium chloride are potentially dangerous. Friedman[3] and his colleagues warn that cation resins should be used cautiously, if at all, in patients with kidney disease or renal insufficiency.

a. *Infection.* Sometimes a febrile illness will cause edema to disappear with miraculous rapidity, but the patient's subsequent state is often far worse. Some of these children have been exposed to measles. This is done at great risk and may add to the patient's discomfort.

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b. *ACTH.*[4] Nephrotic patients are particularly prone to infections due to a general lack of resistance. In a number of children, pneumococcic infections as well as bacteremia has occurred during therapy in spite of the prophylactic use of high doses of antibiotics. When this happens, ACTH treatment must be discontinued until after recovery. The hormone has a tendency to produce edema, raise the blood pressure and elevate the blood level of nitrogenous metabolites. In the majority of patients, administration of the hormone causes an initial weight gain, and often increased urinary protein, associated with a diminished excretion of sodium, chloride and water. Multiple courses of hormone therapy are necessary and diuresis, as a rule, begins after withdrawal of the hormone. Edema does not always completely disappear although urine protein diminishes.

c. *Methionine*[5] is a synthetic sulfur-containing amino acid. This amino acid plays a strategic rôle in the overall metabolism, participating in fat, protein, sulfur and water metabolism as well as supplying energy. Its versatility exceeds any other known substance.

1. *The Mechanism of Methionine Action on Liver Fats.* Methionine is a lipotropic amino acid.[6] The word lipotropic means having an affinity for fats or oils, and thus acting on the metabolism and transport of fat. The lipotropic action of methionine is said to be due to its ability to contribute its methyl group for the synthesis of choline from ethanolamine.[7]

Choline is an essential precursor of lecithin which favors the transport of lipid materials in a colloidal suspension. Lecithin and cephalin make up the major portion of the lipids in most tissues. In summary, methionine, as a precursor for choline, favors the transport of lipids in a colloidal suspension and prevents fatty infiltration of the liver and probably the kidneys.

2. *Methionine and Transmethylation Reactions.* a. duVigneuad and his associates proved by means of isotopic elements in dl-methionine that this amino acid contributes its labile methyl group for the conversion of guanido-acetic acid to creatine. Creatine is important in muscle physiology.[8]

b. The lipotropic action of methionine is apparently due to its ability to contribute its labile methyl group for the synthesis of choline from ethanolamine. The methionine molecule contains only

one methyl group, consequently at least three molecules of methionine are required for one choline molecule.

3. *The Mechanism of Methionine Action on Protein Metabolism.* Methionine spares nitrogen.[8] This is equivalent to "nitrogen retention." In relation to amino acid metabolism, "nitrogen retention" has derived a connotation in which sense it will be used in this discussion. In this sense it means a diminished excretion of nitrogen as urea and ammonia. Depressed nitrogen excretion is the result of accelerated amino acid utilization for protein synthesis. It is not the same "nitrogen retention" or "azotemia" caused by kidney disease.

The utilization of amino acids for building up tissue is a very rapid process. For purposes of tissue synthesis, each essential amino acid must be available in adequate quantity at approximately the same time.[9]

Maintenance, repletion, tissue repair, detoxication, antibody formation, erythrocyte production, growth, essential structural proteins, as well as important functional units, may require increased quantities of specific essential amino acids to compensate for any variety of severe stress. In case emergency demands for specific amino acids are not covered by the food supply, dispensible reserve stores are raided to supply them.[9]

Supplementary methionine completes the amino acid mixture in the nitrogen pool; permits optimum protein synthesis by virtue of nitrogen retention; depresses accelerated tissue protein breakdown and, in turn, arrests increased non-protein nitrogen excretion.

4. *Methionine and Nitrogen Equilibrium.* Valine, methionine, threonine, leucine, isoleucine, phenylalanine, tryptophane and lysine are necessary constituents of the diet of man. The exclusion of anyone from the diet produces a pronounced negative nitrogen balance.

The body is said to be in nitrogen equilibrium[9] when the nitrogen content of the ingested protein is equal to the nitrogen excreted. Nitrogen equilibria can be established at various levels of nitrogen intake, from as low as 2 gm. per day to 25 or 30 gm. or even more. If the protein consumption is increased above an established level, the normal adult will, after a few days of positive balance, establish a new equilibrium at a higher level of protein intake and excretion. If, on the other hand, the protein of the diet is suddenly decreased, a negative balance results until readjustments

take place. Equilibria are re-established at lower and lower levels.

When the demands for specific amino acids or for proteins are not covered by the food supply, reserve dispensable stores are raided to make available the necessary amino acids.[9] This breakdown is accentuated if the protein stores are also called upon to act as a source of energy.

Supplementary methionine becomes equivalent to a high protein diet. It supplements existing amino acids in the metabolic pool, and makes possible the presence of adequate quantities of each of the essential amino acids available at approximately the same time. This is conducive to tissue and plasma protein synthesis as well as eventual accumulation of reserve protein stores. Nitrogen retention is increased and nitrogen excretion as urea and ammonia arrested. Nitrogen equilibria are gradually elevated to higher and higher levels.

Methionine, therefore, is far superior to urea which is essentially an excretory product offering but few advantages to protein metabolism. Methionine plays a strategic rôle in protein metabolism as well as overall metabolism. In lipoid nephrosis, it should, theoretically, help correct hypoproteinemia, promote diuresis, eliminate edema and improve tissue function.

5. *Methionine and Sulfur Metabolism.* In the absence of an adequate supply of cystine in the diet, methionine is converted to cystine.[10] Cystine is well recognized as a major constituent of hair, nails, hoofs, horns and skin.[11]

Methionine is a precursor of cystine which is an essential constituent of glutathione, of insulin, and of plasma proteins. Its presence in the diet reduces the methionine requirement one-sixth. Its total absence may thereby so increase the requirement for methionine that an inadequate diet may become inadequate by application of the "law of minimum."

6. *Methionine as a Source of Energy.* Methionine may serve as a potential source of energy in the following manner: (1) the direct oxidation of amino acids for energy production, (2) the keto acid remaining after denitrogenation may be converted to glucose (and stored as glycogen) or to fat. This is equivalent to a storage of protein energy, (3) the oxidation of proteinogenous glycogen and fat to provide energy for internal work, later dissipated as heat, and for mechanical work. The labile methyl group of methionine,

in addition, can be oxidized to carbon dioxide thus supplementing energy resources.

7. *Methionine and Detoxification of Toxic Substances.* It has been known for years that high protein diets exert a protective mechanism in animals exposed to certain toxic compounds. The effective agent in proteins against these poisons was found to be methionine.[12] The body may employ methionine preferentially for detoxification, even at the expense of raiding and sacrificing its own tissues to obtain the required material. This may create a relative methionine deficiency.

8. *Methionine and Water Metabolism.* (a). *Edema Due to Sodium Retention.* It has been possible to reduce edema and ascites in many cases of liver disease due to toxic substances and specific nutritional deficiencies.[6] Methionine and choline, therefore, have diuretic properties. In liver disease it is not the utilization but rather the mobilization of lipids which is at fault. Methionine and choline mobilize lipids. This presumably removes lipids from the convoluted tubules. Partially occluded tubules are reopened and restored to normal structure and function. This encourages diuresis, reduces rapid reabsorption of sodium and eliminates edema due to sodium retention.

(b). *Edema Due to Hypoproteinemia.* Hypoalbuminemia is an important feature of lipoid nephrosis. A low level of plasma protein (particularly albumin) with retention of sodium results in edema.

According to Gounelle,[13] hypoalbuminemia, per se, is not the cause of nutritional edema. Edema may exist in the presence of normal levels of serum albumin. Furthermore, hypoalbuminemia may not result until after the appearance of edema.

Animal experiments have proven casein superior to lactalbumin for protein regeneration.[11] Whereas lactalbumin regenerates plasma albumin, casein promotes synthesis of both albumin and globulin. Although casein contains a greater methionine-cystine content, its superiority is said to be due to an alcohol soluble fraction present in minute quantities.[14]

Casein is superior to any other dietary substance which causes the disappearance of edema due to submutrition.[13] This superiority may probably be due to its increased methionine-cystine content.

Edema, therefore, must be contingent on the deficit of one or

more specific substances perhaps in association with hypoalbuminemia. These substances may very well be methionine or other sulfur containing compounds. Be this as it may, methionine helps correct hypoproteinemia and in turn eliminates edema which is believed to be largely osmotic in nature.

(c). *Diuresis Due to Increased Nitrogen Excretion and Acidosis.* Accelerated protein catabolism due to partial starvation or negative nitrogen balance elicited by any stress factor produces relative acidosis with increased excretions of phosphorus, sulfur and nonprotein nitrogen which promote diuresis. When supplementary methionine inhibits raiding of tissue protein for the deficient nutrient, urea excretion is depressed and diuresis eliminated. Furthermore, protein synthesis made possible by the simultaneous presence of adequate quantities of each of the essential amino acids promotes water retention as cell fluid.[9]

9. *Methionine Deficiency and Increased Nitrogen Excretion.* A deficit of dietary methionine produces an amino acid imbalance.[9] Tissue protein synthesis results only when adequate quantities of each essential amino acid are simultaneously available. In the absence of a single amino acid, tissue proteins are raided to supply the necessary methionine for maintenance.[9] The remaining amino acids which by default are inadequate to fulfill protein synthesis[15] requirements are excreted.[11, 16, 17] Amino acids cannot be stored. Those amino acids not utilized for energy are presumably carried to the liver, deaminated and excreted as urea. Methionine deficiency, therefore, depresses nitrogen retention but increases nitrogen excretion.

10. *Excess Methionine and Increased Nitrogen Excretion.* Changes in concentration of dietary methionine probably effect the gain or loss in body weight and of body nitrogen more than any other essential amino acid. Either a deficit or an excess of methionine leads to increased nitrogen excretion and loss in weight.[9] In the experiment animal, for each milligram of excess methionine administered, 1.86 milligrams of nitrogen was excreted in the urine. Roth and Allison[18], as well as Kade and Shepard[19], were unable to demonstrate an imbalance of excess methionine on nitrogen excretion. They did report a loss of body weight (which may be interpreted as a loss of water) in rats fed excess methionine in a low protein diet. When more nitrogen must be excreted as urea, additional quantities of water are required for its transportation.

An optimum of supplementary methionine is conducive to nitrogen retention.[9] Supplementary methionine completes the amino acid mixture in the metabolic pool.

But once the optimum requirements are exceeded by an inordinate quantity of methionine, an amino acid imbalance is recreated. Larger than optimum amounts of methionine increase the excretion of urea causing loss in weight.[9] Still larger excesses of methionine increase the excretion of creatinine as well as urea, reducing the nitrogen in the skeletal muscle.

Although amino acid imbalance produced by adding a large excess of methionine causes a reduction of nitrogen in the skeletal muscle, it increases the size of the kidneys, the plasma globulin concentration and liver nitrogen. Thus while one type of tissue is being torn down another is built up.[9]

Either a deficit or an excess of methionine leads to increased nitrogen excretion but the end results are diametrically opposed. A pattern of amino acids deficient in one or more essential amino acids is catabolized rather than entering into the synthesis of protein. Internal supplementation merely increases nitrogen excretion and adds nothing to protein synthesis. An inordinate excess of supplementary methionine, on the other hand, promotes protein synthesis even though tissue protein is being torn down to supply the missing building blocks in the nitrogen pool.[9]

III. *Physiology of Nephrotic Edema.* The relatively slow passage of the filtrate through the lipid infiltrated tubules permits reabsorption of an abnormally high percentage of sodium (and consequently of water.)[20] This retention of sodium and water contributes to the osmotic edema produced by hypoproteinemia and is an indication for restriction of sodium intake. The very great proteinuria is believed to be due to an increased permeability of the glomerular membrane. The low osmotic pressure of the plasma and the increased glomerular permeability combine to cause an abnormally high rate of glomerular filtration.[21] However, since there is apparently an even greater increase in rate of reabsorption of sodium and water, these substances are retained in the body.

It has been suggested that edema of the kidneys themselves and increased intra-abdominal pressure may, in some instances, contribute to the disturbance in renal function.[22]

Normally, the body's usual daily production of waste products

can be excreted in 600 to 700 cc. of urine per day.[23] If there is excessive production of these substances or a decrease in concentrating power of the kidneys, an increase in urine volume must result to prevent retention.

Methionine and choline are lipotropic substances which mobilize lipids from the liver to the fat depots. They most likely can mobilize lipids from other organs equally as well. In the kidney, lipid-free convoluted tubules are reopened and restored to normal structure and function. This encourages diuresis, reduces rapid reabsorption of sodium and eliminates edema due to sodium retention.

IV. *Pathology of Methionine Deficiency in the Experimental Animal.* Wanscher[24] found that rats on a methionine-cystine deficient diet develop: (1) severe degeneration of liver cells concomitant with hemorrhage and intestinal inflammation, (2) degeneration of the convoluted tubes of the kidneys and (3) not infrequently, severe chronic convulsions.

V. *Case Report.* A girl, aged 2 years 7 months, weighing 16.4 kilograms, was admitted to the hospital with massive generalized edema, ascites and bilateral hydrothorax. Her blood pressure was 112/80 mm.Hg. and her urine contained much protein, few white cells, many hyaline and granular casts but no red cells. Because of the massive edema it was impossible to enter any of the veins for blood chemistry study. She received a low salt, high protein diet with no restriction of fluids for the first two weeks. She also received 0.1 cc. of intracutaneous staphylococcus toxoid (10,000 units per cubic centimeter) every four days for four injections with the object of producing a foreign protein shock reaction without subjecting the child to the risk of a measles infection.

During the first two weeks her weight increased to 18.1 kilograms, a gain of 1191 grams. At this time she was given 9 grains of crystalline dl-methionine daily in three equally divided doses. (Mulcin, a multivitamin preparation prepared by Mead Johnson, was used as a vehicle. Each teaspoonful contained 3 grains of crystalline dl-methionine.)

On the third day of methionine therapy, diuresis became apparent. She lost 1446 grams during the first week and 2070 grams during the second week. Her weight reached 14 kilograms. After four weeks of methionine therapy her weight was 14.7 kilograms.

She was completely free of edema, ascites and bilateral hydrothorax.

After one month of methionine therapy, the urine showed only a faint trace of albumin, 1-2 white cells but no casts or red cells. At this time the blood cholesterol level was 350 mg. per 100 ml., blood urea level 12.9 mg. per 100 ml., serum-albumin level 3.39 Gm. per 100 ml., and serum-globulin level 1.14 Gm per 100 ml. Two weeks later the blood cholesterol level was 319 mg. per 100 ml. and four weeks later 126 mg. per 100 ml.

VI. *Discussion.* About ten years ago Farr and his associates reported that the concentration of amino acids in the blood plasma of cases of lipoid nephrosis was subnormal. This is understandable when we recall the tremendous losses of protein in the urine. This produces hypoproteinemia and is equivalent to protein starvation. A similar situation arises in starvation edema due to: (1) chronic alcoholism, (2) famine and (3) inadequate prison camp diets. In all instances, there may arise edema, ascites and hydrothorax. These pathological disorders may in fact be methionine deficiency since methionine plays such an important rôle in total metabolism.

Fatty infiltration of the liver, due to chronic alcoholism or starvation, may probably be related to lipoid nephrosis. Wanscher found that rats on a methionine-cystine deficient diet develop degeneration of the convoluted tubules of the kidneys in addition to liver damage.[24]

It is more than a coincidence that it required three days to initiate diuresis. In a previous communication, it was shown that methionine eliminated volatile ammonia in cases of ammoniacal urine within a period of three days.[25] In both instances, it indicates the time interval necessary to: (1) promote nitrogen retention; (2) elevate nitrogen equilibrium to a new level; (3) fabricate tissue and plasma proteins and (4) correct relative acidosis.

Methionine is a strategic, versatile amino acid having many properties permitting it to participate in the overall metabolism. Optimum quantities of methionine: (1) promotes nitrogen retention; (2) maintains nitrogen balance; (3) diminishes nitrogen excretion; (4) influences water balance; (5) has lipotropic activity; (6) is important in sulfur metabolism; (7) has transmethylating activity; (8) influences acid-base balance; (9) is important in

detoxification of toxic substances and (10) has glucogenic activity. Its versatility exceeds any other known substance in the body.

VII. *Summary.* The occurrence of spontaneous remission makes the effects of any treatment of lipoid nephrosis difficult to evaluate.

Since all forms of therapy have many disadvantages, a therapeutic trial of large doses of methionine in addition to the conventional low sodium, high protein diet was made. Nine grains of methionine daily in three equally divided doses initiated diuresis on the third day. Within two weeks there was complete disappearance of ascites, hydrothorax and edema. Proteinuria as well as casts disappeared in four weeks. At this time, the dosage of methionine was reduced to three grains daily to promote continued nitrogen retention.

A physician may have the good fortune to treat only one or two cases of lipoid nephrosis in a lifetime. With this in mind, I have described a new form of therapy in the vain hope that it may be repeated, proven valid, or thrown into the barrel of coincidence. Methionine in excess is known to produce diuresis in the experimental animal. I have demonstrated it to myself in several normal children. Theoretically, it should produce diuresis in the child with lipoid nephrosis as it does in cases of ascites due to fatty infiltration of the liver.

VIII. *Conclusion.* Methionine is a versatile amino acid which plays a strategic rôle in the overall metabolism, participating in fat, protein, sulfur and water metabolism. In the case of lipoid nephrosis under discussion, methionine not only eliminated the symptoms but also repaired kidney pathology, reduced hypercholesteremia, replenished plasma protein, and corrected hypoproteinemia, a true clinical cure of a disease having a very bad clinical and statistical prognosis.

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RH INCOMPATIBILITY BETWEEN MOTHER AND CHILD. (Medical Journal of Australia, Sydney, 1: 781, June 2, 1951). This paper presents the results of the serologic examination of a consecutive series of 9,533 mothers and babies in relation to Rh incompatibility. A total of 1,584 women (16.7%) were Rh negative. Of these Rh-negative women, 952 had Rh-positive babies and 8 had stillborn babies who could not be tested but were presumed to be Rh-positive, making a total of 960 (60.6%). Rh antibodies were found before, at, or after delivery in the serum of 71 of the Rh-negative women. In these 71 pregnancies, 19 women were normal. Of the 52 infants who were affected, 10 had congenital edema and were stillborn, 36 had icterus gravis, 5 had anemia, and the condition of 1 was intermediate. The incidence of prematurity was greater than in the average population and ran parallel with the severity of the erythroblastosis. The over-all fetal loss was 14, there being four neonatal deaths in addition to the 10 stillbirths. Of the four neonatal deaths two were due to erythroblastosis, one to atelectasis and erythroblastosis, and one to atelectasis. In a review of the histories of previous erythroblastotic infants in the family, the variations in severity of the disease in successive pregnancies are emphasized. This aspect should be borne in mind in evaluating any therapeutic procedure.—*Journal A.M.A.*

EDUCATION IN PUBLIC HEALTH

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On various college and university campuses throughout the country learned professors endeavor to organize the wisdom of experience into courses. With administrative authority, a certain coalition of courses is labeled a School of Public Health. Within such a school, often deriving support from a School or Department of Education, there are courses which are said to have to do with education in public health.

Looking either at these schools or at experience, the basic thesis of education in public health is the same. Reduced to absolute terms, education in public health refers to educational moves which inform nonprofessional persons in matters of health in such a way that they understand it better. They may apply it to their own health, if they choose, and live with their neighbors and families in a more healthy environment. In this basic raw sense, there is no coercion implied. Choice in acceptance of this education and in its application is voluntary. Under the principles of education, the primary goal of education in public health is a better understanding of the subject, and no more than that.

At the present time, there are concerned with education in public health, the schools, various institutes or institutions, the Government, and health officers. A good many persons in these groups come from schools of public health, if they are not in them already, and these schools make it clear that they would like to have a chance to indoctrinate all who have to do with health. This is only one of the phases in which control of education means control of a great deal more, a point which has yet to be noticed by many of those whose lives are being influenced.

In this realm of education the cardinal principle, education in matters of hygiene and public-health for the sake of understanding them better, has given way in a conspicuous degree to two other techniques, the technique of propaganda and the technique of salesmanship.

The technique of propaganda is one in which a topic is presented in virtually any way which will produce a given change in opinion. The entire intent is to present an idea in such a way that the

listener will be converted to a given viewpoint. Believing intensely enough in that viewpoint, emotional users of propaganda rationalize that it is worth a sacrifice of truth, if necessary, so long as the end result is worthwhile. Political users do not themselves believe in their rationalizing, but use propaganda to gain an end.

The technique of salesmanship is more specific and is built around the thought that the buyer must develop a desire for a given thing. The sale is the important thing, and, in the better circles, only legitimate articles are sold. The presentation of the article for sale, however, must be slanted in such a way that it will sell, a point of view which is not properly permissible in education.

The true educational point of view, a presentation of the truth, the whole truth, and nothing but the truth, regardless of consequences, is the only substantial basis for education in public health, as in other things. There is perhaps no other field in which the old adage, that a little knowledge is a dangerous thing, is so well substantiated. The modern specialist in education in public health is often inclined to say that a little knowledge, instead of being dangerous, is better than none, but an examination of motives will often reveal propaganda in the selection of the knowledge offered. Over and over again it becomes apparent that a partial truth is likely to be a distorted truth. The legal phrase, speaking of the truth, the whole truth, and nothing but the truth in order to emphasize the real meaning of truth is significant. It was an outgrowth of experience, based on realization that partial truths are very often designing truths, leading to false or reiterated conclusions. Even without ulterior designs, this distortion is likely.

To mention examples would be easily possible. Once started, most of us would be able to think of many. They are dangerous to bring up because they arouse emotions, and they would be likely to disturb the argument by deviating from the issue. However, everyone is familiar with some of the countless false remedies, often dangerous, advocated with varying motives by neighbors, and reputable men. Less well-known are the selling techniques used to secure volunteers for experiments on human beings, persons with no chance to know what they face. Not a few of the results have been serious and certainly unnecessary. On numerous occasions man's fear of ill-health or death has been used

to extort money, put over an issue, or otherwise gain from an improper presentation of the truth. There are daily instances whereby publicists and the public are coerced into financial and other support of moves which they do not understand, not by honest education but by appeals to sympathy or other emotions. Is it legitimate in public health to lead citizens with partial truths to the support of one man or several men who will rationalize almost anything in the use of the authority or funds acquired? One such institute, for instance, resorted to the subsidizing of books remotely connected with the subject, and there are many such abuses. Since important committee men travel by air the development of a safety device on a plane could be rationalized as a legitimate expenditure for money devoted to heart disease, money secured largely through the activities of propagandists and salesmen in the guise of educators in public health.

We need a good substantial return to ethics and the principles of freedom.

It is ethically improper for those in public health, as emotional, irrational, and subject to error as anyone else, to assume a dictatorship over the populace. A director of public health may believe in a certain vaccine, but it would be necessary to go no farther than the nearest medical meeting to discover that there are imperfections in this vaccine which demand a whole truth, not a fascist decision. The dictator's viewpoint is improper even when he is correct. There is only one legitimate approach, a true educational approach, and it would certainly help if this could begin with the schools and carry on from there. If there is any legitimate field of "public health education," and there must be, it must be devoted to education, not indoctrinating or putting over deals.

A continuous bombardment of topics of health, even by a truly educational approach, automatically becomes propaganda, though where to draw the line is a matter of opinion. Many persons feel that both advertising and publicizing of matters of health are objectionably continuous. They argue that public health should make possible a communal health without continuous public stewing and fretting. That is secondary to the point here, however. The primary point is that education in public health, in whatever degree, must be presented as the truth, the whole truth, and nothing but the truth without coercion of any kind. The recipient must be

capable of understanding this whole truth; otherwise the truth is distorted and it is improper to present it. He must be free to receive it in any way that he wishes. The objective is not the sale of a given move or the guided acceptance of a given philosophy. The ethical objective can be only education in its purest sense.

To this end, let us beware of salesmen who claim that public health is purchasable. Let us beware of the enthusiasts whose moral decisions are daily weakening as they seek human volunteers for experiments to satisfy their curiosity. Let us be cautious with regard to those who use exotic stories in dramatic appeal to our sympathies and fears, primarily to put over an idea they want to sell. Let us even be wary of uninhibited soliciting for funds for, in too many instances, large percentages of these funds are devoted to moves quite unrelated to the purposes for which the donors subscribed. Those who give so freely of their time in order to secure these funds do not understand this and are not told.

By "us" I refer to the citizens at large, including those in public health, but, it is to those in the field of education in public health that the message is important. On grounds of common decency, on grounds of freedom, and on grounds of morals or ethics, education in public health should be presented as true education, designed for understanding, without salesmanship or propaganda. Only when there is need for it and only when we can present the truth, the whole truth, and nothing but the truth, so help me God, can this education be justified.

PURULENT MENINGITIS IN INFANTS. (Archivos de Pediatria del Uruguay, Montevideo, *22*: 33, Jan. 1951). Bonaba and Portillo report good results from a combined treatment of sulfadiazine by mouth and penicillin and streptomycin intramuscularly in 28 cases of purulent meningitis. Most of the patients were infants and young children. At the beginning of treatment the daily doses per kilogram of body weight should be 50 mg. of sulfadiazine, 50,000 units of penicillin, and 50 mg. of streptomycin. Further doses should be adjusted to the clinical course of the disease, the changes of the cerebrospinal fluid, and the levels of the aforementioned drugs in the cerebrospinal fluid. In the cases reported there were no complications, sequelae, or deaths.—*Journal A.M.A.*

PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

RECURRENT VOMITING*

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SYNONYMS. Cyclic vomiting, lithemic vomiting, periodical vomiting, bilious vomiting. In the present state of our knowledge it is probably best to retain the name "recurrent vomiting," originally used by Gee in describing these cases.

DEFINITION. Recurrent vomiting is a symptom group closely related to migraine. It is autotoxic in origin and characterized by recurrent attacks of nausea, persistent vomiting, and great prostration.

ETIOLOGY. (1) *Predisposing Causes.—Age.* The great majority of these cases occur during infancy and childhood. The disease may make its appearance as early as the third month, but it is more common between the third and tenth year. The tendency is to spontaneous recovery, but the attacks may continue into adult life, or they may be transformed into migraine.

Sex has little influence. A small majority of the cases, however, occur in girls.

Season. It is somewhat more common in winter than summer.

Heredity is the most important predisposing factor. A family history of *migraine* or gout is present in nearly every case. A general neurotic inheritance is common and a family history of hereditary recurrent vomiting is sometimes noted.

Constipation. Nearly all of these patients are constipated and there can be little doubt but that this is an important factor in their etiology. The constipation with the resulting intestinal toxemia no doubt contributes to the general irritability of the nervous system in these cases.

Habits of Life. Mental overwork and nerve excitement, when

*Reprinted from ARCHIVES OF PEDIATRICS, 21: 881-891, Dec. 1904.

combined with an indoor life and confinement in ill-ventilated schoolrooms, are important predisposing factors.

Station in Life. Nearly all these cases occur among the hereditary rich and refined. The poor and uncultured are comparatively exempt. This probably means that the hereditary gouty tendency, with the mental overwork and nerve excitement, which is so common among cultivated people, are such important predisposing factors that the poor and unrefined, in whom they are rare, are not especially predisposed to this disease.

(2) *Direct Causes.* Nearly all writers are agreed that recurrent vomiting is an autointoxication. My own belief is that both auto and intestinal toxins may play a rôle in producing this symptom group, but I do not believe that it is always produced by the same auto or intestinal toxins. I am of the opinion, however, that the largest percentage of these cases is produced by toxins, either closely related in their formation to or identical with the purin bodies. The close hereditary relationship which exists between this condition and gout and migraine lends strong evidence in support of this view, and the urine findings elsewhere noted strengthen this opinion.

The acid intoxications which occur during the attack are to be considered rather as effects than causes, and belong, therefore, to the symptomatology and pathology, rather than to the etiology.

Liver Incompetency. A functional incompetency of the liver is, I believe, an all-important factor. The liver in these cases is probably, by heredity, functionally incompetent, and in addition to this it is perhaps called upon by reason of the constitutional gouty taint to do an unusual amount of work in converting ammonia and the purin bodies into urea. Under these conditions we have periods of temporary functional incompetency on the part of the liver, and as a result the auto and intestinal toxins are poured into the general circulation, and produce in some instances recurrent vomiting, and in other instances migraine. In a few days, when these poisons have been eliminated and the liver has resumed its function, the acute attack is over.

(3) *Exciting Causes.* Mental and physical fatigue, mental excitement, nervous strain, fright, anger, and disappointment are common exciting causes. Over-eating is one of the most potent of the exciting factors and *acid* fruits, berries, vegetables and

wines may precipitate an attack. Intestinal toxemia and reflex irritation from the intestinal canal, the eye, nasopharynx, and genitourinary organs may also be classed among the exciting causes. These exciting factors are at times apparently so important and so definitely related to the onset of the attack that the physician may be inclined to overestimate their importance and thus misinterpret the true nature of the disease. It should always be kept in mind that in these patients, there is a tendency to the recurrence of autointoxications, which are the true causes of the attack, and the particular reflex factor which happens to touch off the paroxysm is not to be considered as the all-important causative factor.

SYMPTOMS. Prodromes are almost always present from a few hours to a few days before an attack. Among the more constant warning symptoms are flushings of the cheek, coryza, general restlessness, nervous irritability, sleeplessness, sallowness of complexion—dark rings under the eyes, general malaise, constipation, coated tongue, a peculiar odor to the breath and loss of appetite. Not all of these prodromes are present in any one case, but in the great majority of cases the mother or nurse, having observed the onset of other attacks, will recognize by certain of these warning symptoms that a paroxysm or recurrent vomiting is imminent.

Vomiting. Following the prodromes, from six to forty-eight hours, vomiting occurs. This is the most characteristic and prominent symptom. In the beginning the vomiting may not be severe, food only being rejected; in a few hours, however (six to twenty-four), it becomes very severe, and accompanied by more or less constant nausea, not only everything that is taken into the stomach is rejected, but bile and much mucus sometimes tinged with blood is expelled. In severe cases the vomiting is accompanied by violent retching, and is oft-repeated without apparent cause. The severe vomiting may continue from one to six days, and then as a rule disappears as suddenly as it came, and with its disappearance convalescence is established. Following an attack the stomach, as a rule, resumes its functions, and within five or six days the patient is taking his ordinary food, without the slightest discomfort on the part of the digestive organs. From this time on the patient rapidly regains his health and strength, and may manifest no gastric symptoms whatever, until the next attack, which may recur

within a month, but as a rule the interval is from two to six months. Subsequent attacks are very similar in their symptomatology to the initial attack. They may vary, however, very greatly in severity and duration. The first attack is, as a rule, diagnosed as a case of ordinary toxic gastritis, due to ptomain or other poisoning, and every effort is made to discover in the food, or vomited matter, the cause of the attack. When the second and third attacks follow, in spite of careful feeding and without apparent cause, the physician recognizes their constitutional origin and makes the diagnosis of recurrent vomiting.

While it is the rule that patients who suffer from recurrent vomiting may have in the interval no stomach or intestinal disturbance, yet this is a rule that has many exceptions, especially in patients under five years of age. Many of these are prone to have gastroenteric disturbances at all times from very slight causes, and many of them during the first three years of life have more or less trouble digesting cow's milk. In these cases frequent attacks of gastric indigestion with mild intestinal fermentations will now and then be broken in upon by an attack of recurrent vomiting, and following this acute attack the patient again returns to his usual condition of health. These chronic cases are, I believe analogous to those of chronic migraine described elsewhere, and while they are vastly more common in young infants they may occur at any age.

Constipation which precedes the attack becomes, as a rule, very obstinate during the attack, and owing to the irritable condition of the stomach, which forbids medication, and the arrest of peristalsis which accompanies the attack, it is at times almost impossible to relieve it. When the constipation is relieved by cathartics, or by the cessation of the attack, the discharges are putrid. A few of the cases reported have had loose putrid movements throughout the attack, and this, while unusual, is more likely to occur in very young patients.

Thirst. While there is absolutely no desire for food in most cases, thirst is a striking symptom. The little patients are frequently asking for water, even when it is immediately rejected. When the attacks are prolonged, and when no food or water has been retained for days, the thirst is excessive and there is usually a parched dry tongue.

Emaciation is great in the aggravated, long-continued cases. There are few diseases that produce more emaciation in a shorter period of time. As little or no fluid is retained in many of these cases, the tissues are drained of water, and as a result the general emaciation is very rapid. The abdomen is boat-like or flattened, the eyes are sunken and this, with the anxious expression of countenance, gives the impression of great danger to life.

The prostration in these cases keeps pace with the emaciation. In all cases it is marked, and in some cases so extreme as to demand the most powerful stimulants to tide the patient over the attack.

Fever is present in nearly every case under ten years of age. From this time on fever is less common until in adult life it is, as a rule, absent. The fever occurs early in the disease, often among the prodromes. It may continue for two or three days varying in height from 101° to 105° F. As a rule, after the second or third day, the temperature commences to subside, and in the latter stages may be subnormal. At times the fever subsides very early in the attack, with the onset of severe vomiting.

The pulse is irregular, as a rule, and usually rapid.

The tongue in the beginning may be coated, but in the latter stages of severe attacks is dry. The peculiar acetone odor of the breath becomes more marked as the attack progresses. A few of these cases complain of sore throat during the attack and in these cases the pharynx and tonsils may be irritated.

Respiration may be sighing, or rapid and panting, out of proportion to the pulse and temperature. The respiratory phenomena in this disease are probably due to the direct irritation of these centres by toxins.

Narcotism, which marks the characteristic close of the migrainous attack, is, from my own experience, not uncommon in this condition. Almost nothing is said concerning this symptom in the reported cases. I am, however, of the opinion, that in nearly all of the severe cases there is, in the latter stages, a tendency to somnolence, and that a prolonged sleep, not infrequently, is followed by the first indications of improvement. In the earlier cases of this disease which I reported, I failed to note this symptom.

Gastric Pain is not present during these attacks in children. I believe, however, that in the adult, gastric pain of great severity

may occur, associated with a severe recurrent vomiting. In some of these cases, at any rate, we have a symptom group exactly similar to that of the child, plus the gastric pain, and these painful attacks may occasionally alternate with painless attacks of recurrent vomiting or with migraine. These are, perhaps, the cases of periodical vomiting described by Leyden.

Nervous Symptoms. While patients suffering from recurrent vomiting may be perfectly free from gastroenteric disturbances during the interval, they are, one and all, nervous, presenting variable degrees of general nervous excitability and restlessness. Snow described a case in which convulsions occurred at the onset of nearly every attack, and I have seen 2 such cases. Many of these children are precocious, and this precocity, like the precocity of migrainous children, may, if properly guarded and restrained, continue throughout adult life. The precocity of the gouty child, whether the child be subject to any of the gouty explosive neuroses or not, is to be distinguished from the precocity which occurs in tuberculous children. Children of tuberculous type are usually undersized and whimsical, and their precocity, which is coupled with physical inferiority, is fitful and sadly lacking in symmetry. The mental precocity of the gouty child, however, does not necessarily mean physical degeneracy, and it may, if properly treated, be sustained and continued throughout the life of the individual.

Urine. The urine, in a case described by Holt, resembled that passed during an attack of migraine. It becomes more scanty as the attack progresses. It is very concentrated and strongly acid in reaction. This acidity causes a rather heavy deposit of uric acid and urates, although the percentage of uric acid is not increased. The xanthin bodies, however, are in great excess. Albumin may be present in small quantities during the attack, although this is rather uncommon. Acetone and indican are present in perhaps all of the severe cases. Many obsevers have found acetone in the urine of these cases, and Marfan published a series of cases, which he described as "vomiting with acetonemia," and suggested that acid intoxications may be a phase of this disorder. More recently Edsall found not only acetone, but diacetic acid and oxybutyric acid in the urine of a number of these cases.

DIAGNOSIS. The diagnosis of recurrent vomiting is easily made if the above symptom group is kept in mind. No disease presents

exactly the same picture. In the atypical cases, however, and especially in the first attack, there may be considerable difficulty. But after the second and third attacks the nature of the disease is made plain. In the first attack the condition is most commonly mistaken for a ptomain or other toxic gastritis. The intestinal symptoms, however, which develop in gastritis, and the cessation of the vomiting under starvation and proper treatment should enable one to make the diagnosis.

Intestinal obstruction, as Griffith suggests, may probably offer the greatest difficulty in differential diagnosis, but the absence of pain and of bloody mucus in the stools and of any tumor, with the presence of the characteristic symptom group, above described, should be sufficient to clear the diagnosis.

The presence of acetone in the urine with the other urine findings, above noted, would assist in making the diagnosis.

PROGNOSIS. The prognosis, so far as recovery from the attack is concerned, is good. The vast majority of these cases recover. It should be kept in mind, however, since a number of fatal cases have been reported, that there is a possibility of a fatal ending. The prognosis, so far as the prevention of these attacks, is also good. Most of these cases can be cured, and all of them can be greatly benefited. Under proper treatment the attacks cease, and the child's general neurotic condition greatly improves. This improvement goes on, and as the child grows older its nervous system becomes more stable and the tendency to these recurring attacks is overcome. In the untreated cases these attacks may be transformed into migraine or epilepsy.

PATHOLOGY AND NATURE OF THE DISEASE. Little is known of the pathology of this disease. An autopsy reported by Griffith showed necrotic changes in the mucous membrane of the stomach and intestine, and slight parenchymatous alterations in the pancreas, spleen and kidneys and fatty infiltration of the liver. Our present knowledge of this condition justifies us in the belief that the disease is an autointoxication, produced by toxins closely related, or identical with the purin bodies, and that a secondary acid intoxication occurs, which may contribute to the symptom group in the later stages of the attack. The autotoxins in this condition select the vomiting centre in the medula as their point of attack.

The close family relationship which exists between migraine

and recurrent vomiting has been previously noted, and I wish here, especially, to note the fact that I have records of 4 of my own cases where typical attacks of recurrent vomiting were changed into typical attacks of migraine, as the children grew older.

In the present state of our knowledge, acetonuria means an excess of diacetic and oxybutyric acid in the urine, we may infer, therefore, that in all of the reported cases in which acetone occurred in the urine, these acids were also present. Von Noorden says: "Owing to the fact that this acid (oxybutyric) is so closely related chemically to acetone and diacetic acid, one is justified in suspecting its presence in the urine whenever these two bodies are excreted in considerable quantities. As a matter of fact, one always succeeds in finding the acid under these circumstances." In the light of these observations published reports warrant the inference that acetonuria, with at least a mild degree of acid intoxication, occurs after the onset of the attack in perhaps all of the severe cases. The acid intoxication, however, is in this disease, as it is in many others, a purely secondary pathological process. Von Noorden believes that all acid intoxications, produced by the presence in the tissues of acetone, diacetic and oxybutyric acids, are due largely, if not wholly, to an insufficient intake of carbohydrates food, or to some fault in the carbohydrate metabolism. A study of acid intoxications reveals the fact that this form of secondary autointoxication very commonly occurs in diseases which produce profound nutritional disturbances. In recurrent vomiting, therefore, we have all the conditions necessary to produce acid intoxications; first, an insufficient intake of carbohydrate food; second, profound nutritional disturbances, and third, faulty carbohydrate metabolism produced by the functional incapacity of the liver. The acid intoxications in this condition are, therefore, secondary rather than primary. It may further be noted that the characteristic symptom group which this disease presents is not that of acid intoxication, but in the later stages of this disease, when the acid intoxication is more marked, it is possible that the respiratory disturbances, the increased pulse rate, the lowering of the body temperature, and the tendency to somnolence may perhaps be partly due to this intoxication.

TREATMENT. *Of Attack.*—If seen in the prodromal stage, ¼ of a grain of calomel, and 5 grains of bicarbonate of soda, should

be given every half hour until 2 grains of calomel are taken. And if the stomach be not too irritable, the calomel should be followed in two or three hours by a saline laxative, and four or five hours later by benzoate of soda in from 3 to 8 grain doses every two or three hours, dissolved in essence of pepsin and peppermint water. No food whatever should be given. Water may be allowed if the stomach will retain it.

After the attack is well on the nausea and vomiting preclude not only all food but all stomach medication. The calomel and bicarbonate of soda, however, may be tried at any stage of the attack, and if the nausea and vomiting are not greatly aggravated by them they may be continued. At intervals throughout the attack, water may be allowed, even though the stomach rejects it, but no food is to be given until the patient is able to retain water in small quantities.

In cases where food and water are not retained by the stomach it is advisable to give, at intervals of every eight to twelve hours, a high rectal enema of physiological salt solution, or bicarbonate of soda solution, a tablespoonful to the pint of water. The tissues, as a rule, are so starved for water that these solutions are absorbed, and the water thus absorbed serves to flush out the various excretory organs and in this way promote the excretion of autotoxins. The bicarbonate of soda given by the rectum, or the mouth, serves the purpose of neutralizing acids; thus removing or preventing the secondary acid intoxications which occur in these cases. Edsall's suggestion that very large doses of bicarbonate of soda be given by the mouth is a good one in those cases in which the soda is retained, but my experience is that the cases which need this treatment most are the ones which retain nothing on the stomach.

In the most aggravated cases where prostration is extreme, and stimulation strongly indicated, sterile physiological salt solution may be injected into the subcutaneous tissues. In cases of this kind, also, it occasionally becomes necessary to give morphin hyperdermically. This remedy acts specifically in the control of the vomiting, and in the worst cases it is a life-saving measure. Small doses of from 1-10 to 1-20 of a grain, depending upon the age of the patient, are usually sufficient.

Curative Treatment. It will be found that many of these children prefer an indoor life and intellectual pursuits. For habits of

this kind, an outdoor life, with moderate exercise, in the open air and in a suitable climate, should be substituted. Since these cases occur very commonly among the well-to-do, it is often possible to prescribe an outdoor climate the year around. Our southern states, and especially southern California, are admirable winter climates for these children, while the region of the Great Lakes, or the sea-coast of our North Atlantic States, offer favorable climatic conditions during the summer. Sea voyages are also beneficial.

It should be remembered that while the climatic treatment of many of these cases is important, it does not take precedence over the medical, dietetic, and general hygienic treatment, which may be carried out in any climate; and my experience leads me to believe that these cases do better at home during the greater portion of the year, provided the home offers favorable opportunities for carrying out the general treatment here outlined. But even where the treatment is carried out under favorable home conditions a change of climate for a few months during the year is advisable, and by this change the hot months of summer or the cold of winter may be avoided, as the climatic conditions at home may dictate.

These children should, as a rule, be taken out of school, and lead as quiet and uneventful lives as possible. Mental stimulation, nervous excitement, and all forms of mental and physical fatigue are to be avoided for a number of years, or until the child's physical and nervous condition justifies a return to the ordinary routine of child life.

Diet. The diet should be carefully restricted, and selected. In beginning the treatment all raw fruits, acid vegetables, such as rhubarb and tomatoes, salads, tea, coffee, beef-juice, beef tea, and alcohol, are to be avoided, and the child should be allowed to eat but sparingly of beef and sweets. The following foods may be allowed: Milk, cocoa, vegetable soups, cereals, well-cooked vegetables, cooked fruits, eggs, fish, chicken, mutton and, occasionally, beef. Children suffering from recurrent vomiting have, as a rule, in the interval between the attacks, abnormally large appetites. They are, therefore, to be carefully guarded against taking an excess of food of any kind, and are to be made to cultivate the habit of drinking water between meals.

Medical Treatment. Before beginning the medical treatment sources of reflex irritation should be carefully sought for, and, if

possible, removed. Constipation, which is constantly present in this condition, demands our most thoughtful consideration. It must be relieved. This can usually be done by palatable solutions of sulphate and phosphate of soda. These saline laxatives are advisable in the beginning of the treatment. Later, palatable mixtures of rhubarb and cascara sagrada may be used. Enemata are not to be relied upon in the treatment of this condition. Abdominal massage may sometimes relieve the constipation and, where it is necessary to resort to massage for this purpose, it is advisable to give the patient general massage at the same time.

In patients of feeble constitution, so situated that an outdoor life with moderate exercise cannot be had, general massage is a very valuable remedy, apart from the influence it may have upon constipation.

In the medical treatment of this condition, however, the wintergreen salicylate of soda and the benzoate of soda, put up in palatable solution in a dose to suit the age of the child, are our most valuable remedies. The following prescription will be found of service:

℞—Sodii salicylatis (gaultheria) ..... ℥i
Sodii benzoatis ..... ℥ii
Pepsin essence ..... f℥ii
Aquæ menth. pip ..... f℥ii
M.S.—Teaspoonful after meals for a child six years of age.

In the more severe cases this prescription must be continued for months at a time, and, after this, is to be given once a day for an indefinite period.

The general treatment here given is principally the same as that outlined by me in 1898, in the "American Text Book of Diseases of Children," and many years of experience have taught me that under this treatment the prognosis, even in the most severe cases of recurrent vomiting, is good not only as to the prevention of attacks, but also as to permanent recovery.

BOOK REVIEW

FUNCTIONAL ENDOCRINOLOGY FROM BIRTH THROUGH ADOLESCENCE. By Nathan B. Talbot, M. D., Edna H. Sobel, M. D., Janet W. McArthur, M. D. and John D. Crawford, M. D. Cloth. Illustrated. Pp. 638. Price $10.00. Harvard University Press: Cambridge, Mass., 1952.

This book is an excellent study of the physiology and its clinical application of the endocrine glands. At times the physiological discussions and complicated charts become a bit heavy, nevertheless a careful reading gives one a better understanding of the functioning of the endocrine glands and their pathological behavior becomes clearer and understandable. The book once read becomes a valuable reference source. Although the volume is replete with excellent illustrations, the authors failed to include one of hyperossification as found in hypoparathyroidism. The book contains a wealth of information, some of which comes immediately to mind. In discussing hypothyroidism, the authors note that these persons tolerate morphine poorly and that they are apt to develop laryngeal spasm which may stimulate mechanical upper respiratory obstruction. In the chapter on the adrenal cortices, we are reminded that all instances of masculinization developing postnatally and before the age of 10 years were due to adrenal tumor; however, with only few exceptions, cases of masculinization which appeared to date back to birth were caused by benign bilateral hyperplasia of the adrenal cortex. The menarche is frequently approached with anxiety, hence it is well to remember that the adolescent must experience approximately 40 menstrual cycles before the periodicity characteristic of the mature woman is achieved. A lenient view of adolescent irregularities should therefore be adopted, and hormone therapy employed with the utmost restraint. Unwise interference may jeopardize the establishment of the mature pituitary-ovarian-uterine cyclic relationship upon which normal menstruation depends. The book is highly recommended as being very informative.

MICHAEL A. BRESCIA, M. D.

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